A Call to Action: Immediate Deployment Of Select Repurposed Drugs For COVID-19 Outpatient Treatment

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At the time of this writing approximately 3,000 Americans are dying of COVID-19 each day. While new cases have dropped off from a previous surge of 150,000-250,000 daily that was associated with holiday travel and increased indoor gatherings, the spread of new, more contagious variants of the coronavirus that causes COVID-19 threatens to reverse this reprieve. Health care systems could again face collapse and our economy is hurting badly.

The world embarked on an aggressive plan for developing effective vaccines which undoubtedly offer the best long-term solution to the COVID-19 pandemic. However, it will be mid 2021 before vaccine administration will show much impact and only if we resolve issues around delivery logistics, access and acceptance. Also, there will always be the threat of resistant strains evolving, the possibility of unexpected toxicities, and the uncertainty of how long the vaccine will be effective.

Thus, we desperately need approaches that can be deployed now and have the potential to save 100,000 to 150,000 lives in the next few months. We believe the approach we outline below can meet this need. But we also believe that, unfortunately, COVID will not be the last infectious disease threat the world faces, and the strategy we propose could be used to address future pandemics.

Repurposed drugs deployed nationally and evaluated by real world data

To have impact, any solution must be affordable, scalable, feasible, efficacious, safe, and—most importantly—immediately implementable.

Remarkably, a handful of drugs approved by the Food and Drug Administration (FDA), listed below, have shown promise in treating COVID-19 patients. These drugs have established safety records since they have been prescribed to millions of patients, and many are in chronic use. Given the minimal risk and the current state of the pandemic, shouldn't COVID patients, if they so desire, have ready access to these drugs "off-label"?

We believe the answer is yes and suggest immediate deployment of select FDA-approved drugs in the early outpatient COVID setting as important options that should be readily available—in addition to monoclonal antibodies, currently approved for those at highest risk for disease

progression. Such a strategy could dramatically reduce the number of patients requiring hospitalization in a matter of three-four weeks.

The gold standard for adopting new treatments is to conduct large randomized controlled trials (RCTs). Such studies, typically sponsored by pharmaceutical companies for new drugs, are time consuming and expensive. For an off-patent drug, manufacturers have little financial incentive to repurpose for another use. Academic clinicians do conduct such trials but due to limited resources and time, it often takes a long time to enroll a full complement of subjects.

A newer version of such studies, often referred to as a decentralized trial, can be used to enroll patients nationally in a trial run by a single health center through the use of telemedicine, but here, too, enrollment may be a challenge. Therefore, in a pandemic situation, these approaches may not offer timely results.

Real-World Data Contributing To Real-World Evidence

The National Institutes of Health, the Centers for Disease Control and Prevention, or FDA could issue temporary use guidance encouraging the repurposing and off-label prescribing for COVID-19 of existing drugs. The guidance would include inclusion and exclusion criteria, drug dosing, schedule, patient monitoring requirements, and an informed consent form. This approach would allow any doctor and any patient, irrespective of location, to immediately participate, allowing rapid enrollment of a diverse 'real world' patient population in rapid order.

The idea is similar to an Emergency Use Authorization (EUA), but an EUA does not typically provide tools for collecting patient data and for monitoring and evaluation of drug safety and efficacy. Under our approach, the temporary practice guidance would be coupled with one or more tools to track outcomes, such as the FDA-sponsored CURE ID app; a small 'stipend' to incentivize physicians to report their real-world patient data; and an analytics team to mine the data in real time and monitor outcomes and adverse events (e.g. clinical deterioration or improvement, hospitalization rate, mortality rate), so that the temporary use guidance can be terminated or modified.

Our proposal is most akin to France's Temporary Recommendation for Use, a "regulatory instrument which aims to allow, on a temporary basis, the use of a medicinal product to allow its effectiveness to be evaluated on the basis of its use." This strategy not only offers patients treatment options they may not currently have, but it promises to rapidly transform real-world data into real-world evidence.

Unpacking The Model

Advantages

Under our approach, a large network of primary care physicians could be engaged to treat patients in the community. Off-label use is legal in the US provided there is some supporting medical evidence; it should be a shared and highly individualized decision between patient and caregiver However, off-label use without RCT level data is generally frowned upon, evokes liability concerns and is variably reimbursed. Our approach mitigates legal as well as medical risks via standardization and outcomes assessment, issuance of an informed consent form, and guidance at a national level.

Furthermore, rapid enrollment of adequate numbers of diverse participants could potentially overcome the drawback of non-randomization our approach entails. It is worth noting that tightly controlled clinical trials may sometimes not simulate real world conditions. Finally, several drug combinations could be assessed simultaneously under our approach; the front-runner could then move to a large randomized trial if necessary.

Potential Concerns

Our approach will not work for all drugs. Oral drugs with few well-characterized drug-drug interactions and known minimal toxicities are best suited to this approach. By contraste, if a drug is rarely used in clinical practice, many physicians will not be familiar with its use.

Our strategy might expose more patients to ‘adverse effects’ than a randomized trial. Near real-time safety monitoring by a central analytics team and selection of non-toxic interventions would reduce this risk.

Real world data collected in this manner may not be conclusive. While this is a valid concern, it could be overcome if we design a simple data collection tool to capture relevant outcomes and enroll large and diverse populations.

Other Considerations

Who Pays For The Drug And Any Specialized Monitoring Needed?

Existing, off-patent drugs are inexpensive, and we suggest that candidate drugs be chosen in part based on having known risk profiles and thus minimal need for expensive monitoring. A fund to cover costs may be needed in case insurance companies do not pay. However, if Medicaid/Medicare agree to pay, insurance companies will likely follow.

Might Our Approach Make It More Difficult To Enroll Patients In Clinical Trials Of That Drug?

Those who might oppose this strategy may point to the hydroxychloroquine (HCQ) story. The FDA issued an EUA for HCQ to treat COVID patients in April 2020. But clinical trials were also initiated and did enroll a full complement of subjects. Once it was clear that HCQ was not effective, the FDA revoked the EUA in June 2020. Moreover, the real-time outcomes data monitoring we are proposing might actually inform the design of the RCT for the drug, e.g. by suggesting a population subset that might respond.

Who Will Champion The Real World Trials?

FDA in collaboration with the National Center For Advancing Translational Studies (NCATS) has launched the Cure Drug Repurposing Collaboratory (CDRC), which may be ideally suited to champion outpatient COVID-19 real world trials. This group has deliberated on the need for rapid implementation and readout, especially for infectious diseases. The release of the CURE ID app where clinicians report novel uses of existing drugs is an example. So, by providing treatment guidance, a simple tool to capture the data, and compensation for time, the CDRC could facilitate rapid testing of 'financial orphans', an example of which is off-patent drugs without a current champion.

Quicker Action?

While government agencies are best situated to take the lead in our approach, we acknowledge that this may take time to stand up because it may necessitate a change in the US drug regulatory framework. An approach that could be immediately implemented is for a few large health care systems to take the lead. By issuing a temporary use guidance for the promising marketed drugs, they could encourage their network of physicians to prescribe 'off-label' treatments in a standardized manner, ideally with an informed consent form. They could insist that the clinical records of patients treated in this way be anonymized and then analyzed for adverse events and clinical efficacy outcomes—all after suitable Institutional Review Board approval. A local patient registry could also be set up.

Repurposed Drug Candidates And Prioritization

Published papers relevant to COVID-19 suggest 100 or so potentially efficacious marketed drug candidates, based upon in silico and in vitro analyses. Interestingly, a dozen or so show hints of clinical efficacy in COVID-19 patients, as gleaned from retrospective observational analyses, case reports/series, and phase II studies.

Moreover, if we only select drugs that are commonly used, affordable, oral, have minimal toxicity, and have a plausible mechanism of action for COVID, with supporting animal data in a relevant model, the list narrows even further. Many of these interventions are being tested in clinical trials across the globe. The following are examples of drugs that we believe should be immediately tested in the outpatient setting through the issuance of a temporary use guidance, either at a health care system level or by government decree. This is not an all-inclusive list and is likely to evolve rapidly. Though many trials are ongoing, most are being conducted abroad, some are small and thus may not lead to definitive answers, and many are enrolling slowly, further emphasizing the need for rapidly gathering real world evidence in the manner we suggest.

Exhibit 1. Candidate drugs for testing in outpatient use to treat COVID-19.

Drugs	**Drug category**	**# of ongoing clinical trials**	**References**
Fluvoxamine	Anti-depressant	1 - Phase III	Ref Ref
Ivermectin	Anti-parasitic	36	Summary
Nitazoxanide	Anti-parasitic	20	Ref
Colchicine	Anti-inflammatory	20	Summary
Famotidine	H_2 blocker	5	(REF1, REF2, REF3, REF4)

Source: Authors' analysis

In summary, during a rapidly evolving pandemic, a small group of the most promising FDA-approved drugs could be repurposed for COVID-19 use using temporary treatment guidance by a government agency and/or health care systems. In either case, concurrent with such efforts, tools to track outcomes should be made readily available and data analyzed in real-time. Large RCTs should be pursued in parallel.

This approach would allow our nation to rapidly evaluate the safety and efficacy of existing drugs that are easy to administer, affordable, and readily available. If successful, this approach could *dramatically* alter the course of the COVID-19 pandemic in the next few weeks, while vaccines take effect. It should also be noted that these repurposed drugs may well be efficacious even against SAR-CoV-2 variants that may render current vaccines ineffective, since they are targeting mechanisms likely to be conserved even in the mutant strains.

Finally, COVID-19 is not the first pandemic the world has faced, and it will certainly not be the last. The infrastructure and experience gained from using our approach to address COVID-19 will enable the same strategy to be used against future pandemics.

Authors' note:

The views presented in this blog reflect those of the authors and are not necessarily those of the institutions to which they are affiliated.

BIOSKETCHES

Vikas P. Sukhatme MD ScD is the Robert W. Woodruff Professor of Medicine, Dean of Emory School of Medicine, and Chief Academic Officer, Emory Healthcare since 2017. He completed residency in medicine and clinical fellowship in nephrology at Massachusetts General Hospital and a fellowship in immunology at Stanford University. He held a faculty appointment at the University of Chicago as an Assistant Investigator of the Howard Hughes Medical Institute. He was chief of the renal division in the Department of Medicine at Beth Israel Deaconess Medical Center and Harvard Medical School. Later, he was the founding chief of the Division of Interdisciplinary Medicine and Biotechnology at Beth Israel and Chief Academic Officer, Harvard Faculty Dean for Academic Programs and Victor J. Aresty Professor of Medicine at Harvard. Sukhatme has made contributions in numerous areas of medicine in both basic science and clinical research. He has more than 200 scientific publications cited over 43,000 times. His longstanding interest in cancer currently centers on "outside-of-the-box" approaches for treating advanced cancer and preventing cancer recurrence using repurposed drugs. He is co-founder of a not-for-profit organization, GlobalCures, that aims to promote promising therapies for cancer not being pursued for lack of profitability. These ideas are being advanced at Emory through the Morningside Center for Innovative and Affordable Medicine, where Sukhatme serves as the founding director. Sukhatme received bachelors and doctorate degrees in theoretical physics from Massachusetts Institute of Technology and obtained his MD in 1979 as part of the Harvard-MIT program in Health Sciences and Technology, Harvard Medical School.

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